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Methadone dose as a determinant of infant outcome during the peri and postnatal period

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Summary

Background: Methadone remains the mainstay pharmacotherapy for heroin dependent women across Europe although treatment is not standard and neonatal outcomes vary. **Aim:** We studied pregnant opioid dependent women to compare outcomes during the peri- and postnatal period in infants exposed to methadone in utero. We hypothesized that doses <30 mg methadone/day would contribute to poorer infant outcomes when compared to doses ≥30 mg methadone/day. **Methods:** A retrospective case note study of methadone maintained mother and infant pairs were evaluated. Cases from an inner city Specialist NHS Substance Misuse Service were categorized according to the methadone dose received at delivery: ≤ 30 mg (detoxification dose) or >30 mg methadone/day. Infant outcomes included gestation, birth weight, and mode of delivery, prevalence of Neonatal Withdrawal Syndrome (NAS) and parenting. **Results:** Nearly twice as many infants in the '≤ 30 mg' group were treated for NAS (40% Vs 22.7% respectively). Mothers in the >30 mg' group were significantly more likely to use; crack cocaine (59.1% Vs 20%, $p < 0.044$); drugs by the intravenous route (49.1% Vs 6.7%, $p < 0.054$) and; be referred to Social Services (100% Vs 73%, $p < 0.043$). Half of their infants were placed under protective care. **Conclusions:** Our study suggests differences in outcomes for infants according to the maternal dose at delivery. More detailed assessment during pregnancy and in the perinatal period of the addict lifestyle may be crucial in optimising neonatal outcomes. Further research is needed in this area.

Key Words: Pregnancy; methadone; high-risk infants; Neonatal Abstinence Syndrome (NAS)

1. Introduction

An estimated 30,000 pregnant women are said to use illicit opioids each year in the European Union [10] but prevalence data is often unavailable or collected in such a way as to make comparisons difficult [24]. In Spain 16% of mothers giving birth had used illicit drugs during the third trimester of their pregnancy although only 2% of the mothers had reported drug use during their pregnancy [9], whereas in the Czech Republic a prevalence of 1.8% illicit drug use was reported among mothers delivering between 2000 and 2009 [24]. In the UK, according to the Advisory Council on the Misuse of Drugs there are between 250,000 and 350,000 children born to substance misusing parents [11].

Opioid drug use during pregnancy is associated with both adverse maternal and neonatal outcomes: maternally including absence of adequate prenatal care and increased risk of contracting blood born viral infections; as a neonate suffering low birth weight [14] symptoms of neonatal abstinence [1, 8, 29], and possible impact on childhood development [20, 21].

Methadone maintenance treatment (MMT) during pregnancy has been extensively studied and is still considered to be the gold standard treatment [7, 15, 22, 27]. The United States, Australia and the UK cite MMT as the best treatment for pregnant substance misusing mothers [23]. It has been demonstrated that methadone on a fixed-daily dose reduces illicit substance use and improves prenatal care, neonatal outcome, and the overall health of pregnant women [25]. However, the benefits can be obviated if inadequate methadone dose is prescribed and heroin is also used

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[14].

The purpose of this study was to compare outcomes in infants exposed to different doses of methadone in utero. We hypothesized that doses ≤ 30 mg (at or below the dose commonly used to initiate detoxification) methadone/day compared to doses > 30 mg methadone/day would contribute to poorer outcomes for infants.

2. Methods

2.1. Study Design and Subjects

A total of 167 pregnant women were identified retrospectively from case notes accessed from a UK inner city NHS specialist drug treatment service. Conditions for inclusion in the study included meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), Revised Fourth Edition [4] criteria for opiate dependence, pregnancy and being older than 18 years of age. To minimise confounding, inclusion was limited to women taking a single daily dose of methadone, with singleton pregnancies, who had been prescribed methadone for at least one month and who delivered at least 24 weeks of gestation. Thirty-seven cases met the study criteria (Figure 1).

To facilitate comparisons, cases were stratified according to the daily dose of methadone prescribed at delivery, namely ≤ 30 mg/day and > 30 mg/day. The rationale for this split was based on the use of this stratification to classify drug use in similar earlier research and national clinical prescribing guidelines related to the recommended dose to begin detoxification [5, 6].

2.2. Ethical approval

This study was approved by the Joint South London and Maudsley NHS Foundation Trust and Institute of Psychiatry, Psychology & Neuroscience (IoPPN)King's College London Research Ethics Committee.

2.3. Instruments

Data was collected on general demographics, detailed social and familial circumstances, and delivery and birth outcomes. The Rivers Scale was used to score neonatal abstinence syndrome (NAS) [26].

2.4. Data analysis

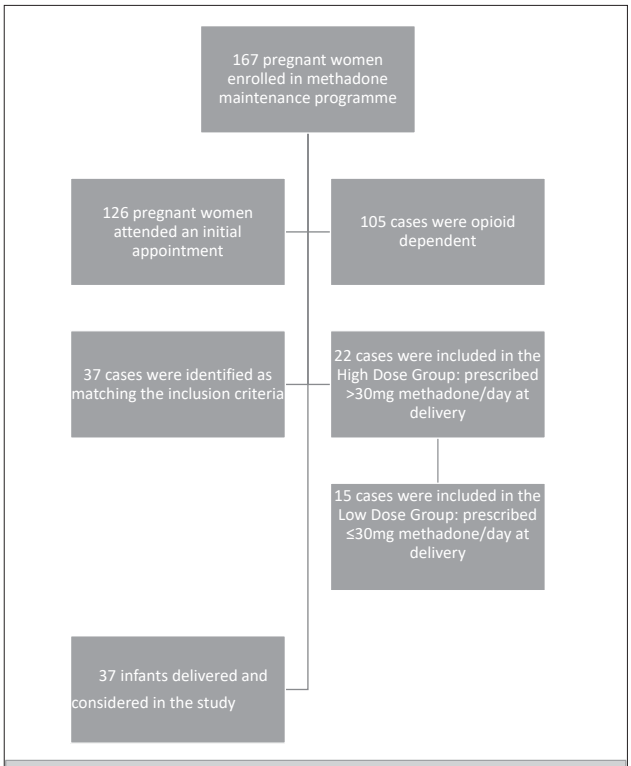

Figure 1. Flow chart of study participants

The independent sample t-test for continuous data and chi-squared test for categorical data was used to examine dose group differences for all demographic and clinical variables. Logistic regressions were performed in order to examine whether there was an independent effect of methadone dose on maternal and neonatal outcomes after controlling for background variables. Statistical significance was set at $p < 0.05$ for all analyses. However, given the small sample size associated with this initial study other levels of significance were also reported. All p values were 2-tailed with corrections for small numbers where $p < 0.05$.

3. Results

3.1. Demographics and methadone maintenance treatment

The mean age of the 37 cases included in the study was 30.2 ± 5.4 years; the majority (76%) of these women were white Caucasian women and 59% lived in unstable accommodation i.e. hostel, or temporary housing. The women were prescribed wide ranging doses of methadone (range 10 mg – 135 mg methadone/day). The daily dose of methadone was not fixed for the duration of pregnancy. The mean

Table 1. Comparison of Maternal and Socioeconomic Parameters for the High and Low Dose Methadone Groups

	Low Dose Group N=15	High Dose Group N=22	p
	n (%) M±sd	n (%) M±sd	
Maternal age	31.9±6.3	28.5±4.5	0.059
Ethnicity (white)	13 (86.7)	15 (68.2)	0.198
Registered with physician	14 (93.3)	21 (95.5)	0.779
Unstable accommodation	9 (60.0)	13 (59.1)	0.956
Care of children	7 (46.7)	8 (36.4)	0.531
Illicit drug use			
Crack cocaine	3 (20.0)	13 (59.1)	0.044*
Prescribed medication	1 (6.7)	4 (18.2)	0.314
Intravenous drug use	1 (6.7)	9 (40.9)	0.054*
Hepatitis C antibody positive	5 (33.3)	5 (22.7)	0.476

Unstable accommodation included hostels, temporary shelter or homelessness
Care of children referred to parental responsibility for other children under 16 years of age
Prescribed medication refers to benzodiazepines (usually diazepam)
* Chi-square with Yates correction for small numbers

dose at initial assessment was 44.7 mg methadone/day; the mode 30 mg/day, prescribed to 18.9% of the group (range 10 mg – 115 mg methadone/day). At delivery, this pattern of dosage had changed. The mean dose had reduced to 38.4 mg methadone/day with the highest dose being 80 mg (range 10 mg – 80 mg) methadone/day: 2 women were detoxified from methadone. Fifteen cases were prescribed ≤ 30 mg methadone/day at delivery compared to 13 women at the initial assessment. Eighteen women (48.6%) underwent methadone dosage reduction during pregnancy, 11 (11%) remained on the same fixed daily-dose and 8 (8%) had their daily dose increased. There was an overall trend towards methadone dosage reduction in the period between initial assessment and delivery, and no relation between change in dose and outcome variable.

3.2. Dosing (≤ 30 mg versus ≥30 mg methadone/day) characteristics

There were few significant differences between the >30 mg dose and the ≤ 30 mg methadone dose groups except in relation to drug use behaviour (Table 1). The >30 mg dose group were more likely to be prescribed benzodiazepines and there was evidence that they were more likely to use drugs via the intravenous route (49.1% Vs 6.7%, respectively; $p < 0.054$). In addition, from the toxicology results recorded from urine drug screening it was found that crack cocaine use was significantly more common among mothers in the ≥30 mg dose group than the ≤ 30 mg dose group (59.1% Vs 20%, respectively; $p < 0.044$).

3.3. Neonatal and perinatal outcomes

The mean gestational age of the neonates was 35.2 ± 3.4 weeks, with 23.7% weighing <2.5kg and characterized as premature. There were more premature infants in those prescribed >30 mg methadone/day, but otherwise growth parameters were similar between the two groups (Table 2). There was no difference in the mean birth weight of infants when dose at delivery was compared (2.9 kg for ≤ 30mg Vs 2.7 kg for > 30 mg methadone/day, respectively) more 'low-weight-for-date' infants in the ≤ 30mg dose group (80% Vs 68.2%, respectively). Although infants in this cohort were almost twice as likely to receive pharmacotherapy for NAS when the maternal dose of methadone at delivery was below 30 mg methadone/day (40% Vs 22.7%, respectively), this did not approach statistical significance (Table 3).

3.4. Postnatal care

When baseline characteristics were controlled, there was no effect of delivery dose on gestational age, type of delivery, birth weight or whether or not the infant was treated in a special care baby unit (SCBU). However, there was some suggestion that women who were living in stable accommodation and prescribed higher doses of methadone were more likely to have full term delivery. Most of the cases (86%) had a community-based health visitor involved in their postnatal care and more than half were seen at home by a midwife (52%). Nevertheless 38% of infants were placed under protective order (regis-

Table 2 Comparison of Maternal and Infant Parameters for the High and Low Dose Methadone Groups

	Low Dose Group N=15	High Dose Group N=22	p
	n (%) M±sd	n (%) M±sd	
Gestation			
Full Term (> 36 weeks)	12 (80.0)	16 (72.7)	0.613
Mode of delivery			
Vertical (SVD)	10 (66.7)	18 (81.8)	
Other (ECS, CS)	5 (33.3)	4 (18.2)	0.292
Neonatal outcome			
Birth weight (Kg)	2.95±0.47	2.67±0.72	0.206
Premature birth	3 (20)	6 (27.3)	
Premature birth weight (kg) <2.5kg)	12 (80.0)	15 (68.2)	0.427
Attended SCBU	4 (26.7)	6 (27.3)	0.967
Infant treated for NAS	6 (40.0)	5 (22.7)	0.259*
Breast feeding occurred	8 (53.3)	10 (45.5)	0.638
Postnatal period			
Midwife seen	8 (53.3)	11 (50.0)	0.842
Health visitor involved	12 (80.0)	20 (90.9)	0.341
Referred to Social Services	11 (73.3)	22 (100.0)	0.043*
Placed on CPR	4 (26.7)	11.50.0)	0.156
Infant removed from parent§	3 (20.0)	7 (31.8)	0.427
Stable accommodation	8 (53.5)	14 (63.6)	0.531

SVD – Spontaneous Vertical Delivery
ESC – Emergency Caesarean Section; CS – Caesarean Section
SCBU – Special care baby unit
NAS – Neonatal abstinence syndrome
CPR – Child Protection Register
§When a child is deemed to be at risk, social services can remove the infant from the parent and place the child in the care of the state with foster parents
*Chi-square with Yates correction for small numbers

tered with a Child Protection Agency) and 26% were discharged into the care of foster parents (Table 2). Women in the '>30mg Dose' group at delivery were significantly more likely to be referred to Social Services (100% Vs 73%, respectively $p < 0.043$).

4. Discussion

In this retrospective case-note study 37 pregnant women who had been maintained on methadone were investigated. When baseline characteristics were controlled, there was no effect of delivery dose on gestational age, type of delivery, birth weight or whether or not the infant was treated in a SCBU. Cases were split into those prescribed ≤ 30 mg/day versus those prescribed >30 mg methadone/day at delivery. It is widely accepted that high-dose MMT provides a 'blockade against other opioids such as heroin during pregnancy and has a positive effect on maternal illicit drug use' [2, 6, 18-19].

The mean dose at initial assessment in our cohort was 44.7 mg and at delivery 38.4 mg methadone/day, too low to achieve a blockade effect and thus although preventing withdrawal our cases continued to use illicit drugs by high-risk routes. The variability in dosing schedules observed in our cases however is not unusual and has been reported in other methadone maintained pregnant populations [23].

Infants in the >30 mg methadone/day group had poor social and familial postnatal outcomes. All mother and infant pairs were referred to Social Services: half of the infants being placed under protective order and 32% removed from their biological mother. It has been shown that children of drug-dependent mothers in foster care have less favourable outcomes compared with those living with their biological parents [16-17]. A further complicating factor was that a large proportion of our cases had dependents under

Table 3. Comparison of Maternal and Neonatal Outcomes for 37 Cases taking into Consideration Change in Prescription of Daily Methadone Dose from Initial Referral to Delivery

	Delivery dose < referral dose N=18	Delivery dose = referral dose N=11	Delivery dose > referral dose N=8	p
	n (%)	n (%)	n (%)	
Gestation				
Full Term	15 (83.3)	1 (9.1)	6 (75.0)	
Pre-term (<36 weeks)	3 (16.7)	10 (90.9)	2 (25.0)	0.486
Mode of delivery				
Vertical (SVD)	5 (27.8)	1 (9.1)	3 (37.5)	
Other (ECS, CS)	13 (72.2)	10 (90.9)	5 (62.5)	0.323
Neonatal outcome				
Premature birth weight (kg)	5 (27.8)	3 (27.3)	2 (25.0)	0.989
Infant treated for NAS	5 (27.8)	5 (45.5)	1 (12.5)	0.291
Breast feeding occurred	10 (55.6)	4 (36.4)	4 (50.0)	0.602

ECS – Emergency Caesarean Section; CS – Caesarean Section
SCBU – Special care baby unit
NAS – Neonatal abstinence syndrome

the age of 16 years: nearly half of the women were responsible for progeny < 16 years of age (46.7% ≤ 30 mg/day dose group vs 36.4% > 30 mg/day dose group, respectively). This is an important complication that requires further investigation [12]. It has been reported that the development of strong patient-provider relationships can improve health care during pregnancy [3].

In our '> 30 mg/day dose' group we found evidence of continuing illicit drug use (cocaine) and intravenous drug use, both of which have been shown to indicate high risk behaviour and potentially a reduced capacity to care for small children [28]. However, the situation is complicated with evidence from Hulse et al [13] in a meta-analysis that the life-styles associated with illicit drug use during pregnancy rather than illicit drug use per se may be the primary risk factor for successful infant outcomes.

4.1. Limitations

As with other retrospective studies, certain limitations are unavoidable and need mention. The primary limitation of this study is the sample size, as only 37 pregnant women were eligible for the study; this limited the interpretation of any association between groups. A larger sample size would be necessary to explore any significant or suggestive findings. Tobacco and alcohol use history were not universally documented. These could also have an impact on the results of the outcome measures.

5. Conclusions

More research is needed in this area and should concentrate on both methadone treatment as well as life-style factors as important variables for women and infants in the post-natal period. Health care providers should advocate approaches informed by scientific research and evidence-based practice to optimise outcomes for mothers and their neonates [29].

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Contributors

K.W., designed the study and wrote the protocol. M.W., managed the literature searches and analyses. J.S., undertook the statistical analysis, and all the authors discussed the results. K.W., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest

Authors declared no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. The study has IRB review/approval.

Note

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